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Update on CJD

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Abstract

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Update On CJD

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INTRODUCTION

In March 1996 the discovery of a new form of Creutzfeldt-Jakob disease (CJD) was announced to a shocked world. In order to understand why this news took the headlines by storm, it is necessary to trace the history of this rare disease and in particular its links with bovine spongiform encephalopathy (BSE), or "mad cow disease". By 1996, Britain had been in the throes of the BSE epidemic for ten years and it was believed that cows had contracted the disease by consumption of scrapie-contaminated food-stuff, scrapie being a similar but much older disease in sheep. Because this represented a species jump from sheep to cows, it was predicted in many quarters that BSE posed a new threat to human health. Therefore the Government took steps to remove BSE contaminated products from the human food chain and the Department of Health set up a surveillance programme to monitor the incidence of CJD in UK. Although CJD occurred subsequently in several British farmers who had BSE amongst their herds, the numbers were not significant and there was no rise in the incidence of CJD in UK above what might have been expected from heightened awareness of the disease and better ascertainment of cases. The Government continued to reassure the public about the safety of British beef but unease

remained widespread and the question of CJD and BSE was never far from the headlines. It was against this background that the sudden appearance in UK of what appeared to be a new form of CJD in 10 young people caused major panic¹. Immediately, the new variant of CJD (nvCJD) was linked in the press with BSE. In fact, there do appear to be some scientific grounds for concluding that nvCJD does results from transmission of BSE, which carries the implication that because huge numbers of people have been exposed to a similar risk, thousands of people may be smitten by this new plague. So what do we know about CJD which might help to determine the likely future outcome? In fact, the story has all the elements of a fascinating scientific thriller - a very rare disease with a long and silent incubation period, a disease both genetic and transmissible, caused by a unique and elusive agent which is apparently capable of replicating itself in the absence of nucleic acid².

CJD IS TRANSMISSIBLE

First described in the 1920s by Creutzfeldt and then Jakob, in a handful of patients (most of

whom turned out subsequently not to have CJD!), the clinical phenotype of CJD was soon defined in terms of a rapidly progressive and fatal dementia. It became clear that the neuropathology of this condition resembled that of scrapie, a disease of sheep that had been known for 200 years. Both were characterised by atrophy of the brain (Fig 1), microscopic vacuolation of the grey matter with accompanying neuronal loss and gliosis (Fig 2) and, in some cases, amyloid plaques. The human and animal diseases were linked under the term, spongiform encephalopathies. In the 1950s, suspicion began to grow that these diseases might be transmissible, especially with the discovery of a similar disease called kuru, in a remote tribe inhabiting Papua New Guinea, who practiced cannibalistic funeral rituals³. This prompted some crucial experiments in which affected brain tissue was inoculated into animals and the transmissibility was confirmed when the recipients developed spongiform encephalopathy after a comparatively long incubation period. In kuru also there was often a delay of years between ingestion of the infected material and the onset of symptoms. Once the tribe were persuaded to abandon their particular funeral practices, kuru became far less common and has now virtually disappeared although one or two cases are still occurring, highlighting the fact that the incubation period may be as long as forty years.

Kuru was the first known example of human to human transmission of a spongiform encephalopathy. Experimental evidence from inoculation of affected human brain tissue into



Fig.1 Coronal section of brain from a patient with CJD showing atrophy and ventricular dilatation.

animals showed that human to animal transmission could also occur. If further evidence was needed that these diseases were transmissible, the occurrence of iatrogenic CJD in the course of medical and surgical treatments certainly confirmed the risk. Iatrogenic transmission of CJD has been reported occasionally following neurosurgical procedures and in patients receiving corneal or dural transplants, but more often in young patients who were treated with cadaver-

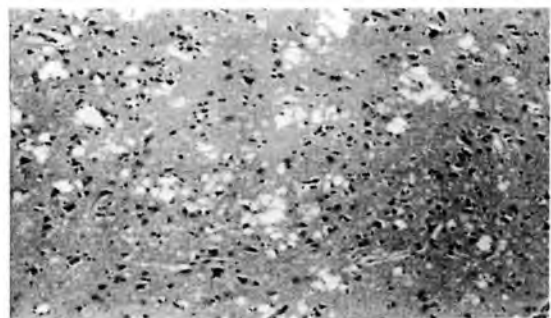


Fig.2 Section of the cerebral cortex from a patient with CJD showing vacuolation of the grey matter. Haematoxylin and eosin x200.

derived human growth hormone prior to the 1980s⁴, some of whom later developed CJD. Symptoms of CJD were manifested in the recipients between two and thirty years after the therapeutic procedure.

CJD IS GENETIC

While all this evidence indicated that the spongiform encephalopathies were

transmissible diseases, it was also becoming clear that in some cases there was a significant genetic component⁵. Although around 85% of CJD cases occur sporadically and in isolation, the remainder have a history of other affected family members. An even rarer form of human spongiform encephalopathy known as the Gerstmann-Straussler-Scheinker syndrome (GSS) occurred only in several very large kindreds and the disease was clearly inherited. Fatal familial insomnia is a more recently recognised member of this group of heritable CJD-like diseases, but does not display spongiform change, rendering the term spongiform encephalopathy no longer appropriate.

GENETIC AND TRANSMISSIBLE - What is the infective agent?

The fact that these diseases could be both transmissible and inherited made them of unique interest and focused attention on characterising the infective agent in the human diseases. Parallel studies of scrapie were in progress both to isolate the infective agent and to identify the genetic background⁶. The genetic locus was identified and named in Edinburgh's Neuropathogenesis Unit as the sip gene in sheep and the sinc gene in mice. Inoculation experiments in which scrapie brain material was injected into mice demonstrated a range of incubation periods and pathology patterns which were very reproducible and which were attributed to strain variations of the infective agent⁷. This was thought at first to be a "slow" virus (slow because of the long incubation period). However despite intensive study, no nucleic acid was ever identified in the infective material used for transmission experiments, leading to the concept of a virino,

this being a very small particle of nucleic acid which was coated with a protein derived from the host animal. While some workers still entertain this concept, current thinking on the nature of the infective agent has swung in favour of the "protein only" hypothesis which has been strongly advocated by Prusiner². In this model, the infective agent is made up of protein (which Prusiner has named prion protein, a term constructed from proteinaceous infective particle). Prion protein, at least in the form which accumulates in diseased brains

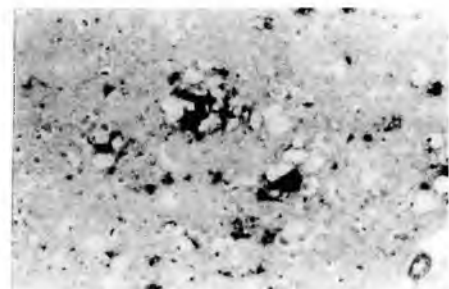


Fig.3 Immunohistochemical evidence of PrP deposition in relation to vacuolation of the cortex in a case of CJD x400.

(Fig 3), is an insoluble, protease resistant protein which is formed by pathological conversion of a normal cell surface protein present in all brains and chiefly on the surfaces of neurones. This protein is of unknown function and is coded from a gene, the PrP gene, which is located on chromosome 20. Work in the last decade has revealed that familial cases of CJD, fatal familial insomnia and all cases of GSS, are associated with mutations in the PrP gene. It also appears that the allelic make up of codon 129 of the PrP gene is peculiarly influential in that homozygosity for valine or methionine at this locus confers susceptibility to the disease both in sporadic and in acquired CJD. To summarise the prion theory briefly, the notion is that in affected individuals the normal soluble form of PrP undergoes a post-

translational modification to an insoluble form which is deposited in different patterns and locations in the central nervous system (Fig 3), giving rise to the characteristic pathology and symptomatic disease. The possession of a PrP mutation makes this change very much more likely to occur so that mutation-bearing individuals have a strong likelihood of developing disease in their lifetime. Cases of sporadic CJD are attributed to spontaneous post-translational modification occurring in the brain of that individual for unknown reasons. In iatrogenic cases, the infective protein may have been introduced directly in contact with the brain (e.g. by dural transplant) and this initiates a relatively rapid onset of translational modification of the host PrP. In patients inoculated peripherally (e.g. injections of infected growth hormone) the agent presumably travels from the periphery to the brain where the pathogenetic change commences somewhat later. The route by which the agent travels from the periphery to the brain is still unknown but may be along peripheral nerves and through the spinal cord, or through lymphatics and involving the lymphoid tissues and the spleen, or by the bloodstream.

Although there is persuasive evidence for the protein-only hypothesis particularly from the spontaneous development of disease in transgenic animals bearing a mutated human PrP gene, there are still some unexplained features such as strain variation⁷, which suggest that other factors may play a part in transmissibility. Many workers in the field consider that variations in pathology and incubation period are governed solely by the host genome which controls expression of the PrP gene and that extraneous nucleic acid is

not required to explain the phenomena of transmission. So far as function of the normal prion is concerned, it is of interest to note that animals in whom the PrP gene has been deleted progress to old age in an apparently normal manner without neurological deficits. These PrP-null animals also fail to develop any signs of disease when inoculated with infective material, confirming that the presence of normal host protein is required as a basis for subversion in the disease state. Whatever the true function of normal PrP proves to be, it is widely expressed in many different tissues and it is somewhat perplexing that pathology and symptoms are confined to the nervous system.

It should be emphasised that the disease is not contagious in the sense of being transmitted by normal contact with affected individuals but requires inoculation or ingestion of infected material to effect transmission.

DECONTAMINATION OF PRION PROTEIN

In addition to eluding exact identification, the transmissible agent displays some unique properties in resisting many of the usual decontaminating agents such as boiling water, ultraviolet radiation, alcohol, nucleases and even formalin fixation and glutaraldehyde. Subsequent experiments have confirmed that the agent is remarkably persistent in the environment and can remain infective after years in the soil. The only measures which are thought to be effective in degrading infectivity include very strong chlorine solutions, strong sodium hydroxide, formic acid, prolonged autoclaving at high temperature and incineration. The remarkably resistant and persistent properties of the agent only add to its mystique and cause enormous problems in

planning for effective removal from the environment or destruction of infected material.

BSE AND HUMAN HEALTH

The appearance of the new cattle disease, BSE, led to the Department of Health asking Dr. R. Will, who had previous experience of this task, to set up a surveillance project for CJD in the UK⁸. This was established in Edinburgh in 1990 and the neuropathological arm of this surveillance project was instituted by the author to confirm the diagnosis of CJD in clinically ascertained cases. Dr J Ironside joined the project shortly after it was initiated. The CJD Surveillance Unit monitored all cases of suspect CJD in the UK from 1990 onwards and sought to identify the risk factors for development of sporadic disease by comparison with suitable controls. A high autopsy rate was maintained and this allowed validation of the clinical diagnosis. Approximately 40-50 cases of sporadic CJD were identified in UK per annum until 1995 when a number of unusually young patients were referred to the Unit with a diagnosis of suspected CJD. These patients had an atypical clinical presentation with a psychiatric onset followed by progressive ataxia and finally cognitive impairment. As the pathology became available through biopsy and then autopsy of these young patients, it became clear that they did indeed display some features of CJD but with a highly unusual pattern of prion deposition which was remarkably uniform between cases. These features included the very widespread appearance of prion amyloid plaques in the cerebral cortex and particularly heavy deposits of prion protein in the cerebellum. By

February 1996, 10 young cases of CJD had been identified with this apparently new pattern of pathology. None of them showed a PrP mutation or had a history suggestive of iatrogenic transmission. They were however all methionine homozygous at codon 129 of the prion gene. Review of previous young cases that had happened occasionally in the past and consultation with European colleagues involved in similar surveillance projects revealed that this cluster of young cases was peculiar to the UK and that the pathology was of a pattern not previously described. Subsequently one similar case has been described in France. This group of young CJD patients was announced in Parliament in March 1996 and published in the *Lancet* in April 1996¹. It was widely assumed that this new variant CJD represented the transmission of BSE to humans and the description of similar pathology produced in macaque monkey brains by inoculation of BSE material only strengthened this hypothesis. Since publication of the initial 10 cases, a further seven cases have occurred in UK but nowhere else in the world. In view of what is known of the incubation period of these diseases, it is impossible to predict how many cases of nvCJD will occur in the future particularly in human hosts of different PrP genotype. Ongoing surveillance of CJD in UK will be required for at least the next decade. Meanwhile the efforts to eradicate BSE from British herds continues and there is no optimism that this will be easy considering what is known of the persistent and resistant nature of the infective agent. Research work is still in progress to establish or refute the connection between BSE and nvCJD and to determine the route by which the infective agent reaches the central nervous system. The

need to develop a clinical test for CJD remains paramount and the recent description of detection of PrP in tonsillar tissue is of great interest both from a diagnostic and pathogenetic viewpoint⁹.

If it is proven that nvCJD is due to the transmission of CJD, the cost to families who have lost young people to a dread disease, and the cost to the Government of millions of animals slaughtered, lost export markets and lost public confidence has been incalculable. It is a sign of the potency of public concern and condemnation that millions of pounds have now been directed to research in this field. Let us hope that this unique group of diseases with their underlying fascinating scientific conundrum remain very rare in the human population.

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Comment:

Clinical Features

The clinical features of nvCJD are relatively distinct from those of the sporadic form of CJD, however, there is some overlap in the presenting symptoms and disease course: the absolute diagnosis is confirmed only by neuropathological tests.

The earliest clinical features of nvCJD occur at a mean age of 29 years. The median duration of the illness is longer than that of sporadic CJD (14 months for nvCJD compared to 4.5 months). Over this period the most prominent features are the psychiatric disturbances or sensory symptoms or both¹. The sensory symptoms reported include foot pain, paraesthesia in the legs and persistently cold feet. Most cases where psychiatric diagnoses were suggested were depressed, apathetic and withdrawn. These initial neurological symptoms are followed by more gross neurological dysfunction, mostly ataxia and a rapidly progressive dementia with involuntary limb movements, urinary incontinence and immobility.

These patients are dependent on continuous nursing care and the development of aphagia may indicate the need for I.V. fluids and artificial feeding. Before death patients are increasingly unresponsive, akinetic and mute.

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